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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/777,743	02/06/2001	Robin Ziegler	5011	8728

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EXAMINER	
GEMENIANO, MALOU C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/777,743	ZIEGLER ET AL.	
	Examiner	Art Unit	
	Malou C. Gemeniano	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 2/6/01.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-32 is/are pending in the application. 24-25, 28-31

4a) Of the above claim(s) 1-6, 8-11 and 13-18 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 7,12, 19-21, 26-27 and 32 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 2/6/01 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse to Group IX comprising claims 7 and 12 filed on 6/18/04 is acknowledged. Claims 1-6, 8-11 and 13-18, 26-28, and 29-31 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/18/04. Furthermore, Applicant added claims 19-32 and asserts that newly added claims 19-32, are properly considered as part of Group IX. However, Applicant does not state clearly how claims 19-32 are part of Group IX. In regards to Claims 19-32, base claim 19 is drawn to method of administering an effective amount of macrophage inhibiting agent such that endocytic or phagocytic activity of the macrophages is inhibited and then administering an effective amount of a gene therapy vector. However, dependent claims of base claim 19 (claims 22-31) are drawn to distinct and independent inventions with varying methods of gene therapy vector to treat patients suffering from different and divergent disease types. In reconsideration of restriction requirement for claims 19-32, Examiner found the following four distinct and patentably independent inventions from the newly added claims:

Group a) Claims 22-23 are drawn to method wherein the patient is suffering from Gaucher's disease and the gene therapy vector encodes glucocerebrosidase

Group b) Claims 24-25 are drawn to method wherein the patient is suffering from Neimann-Pick disease and gene therapy vector encodes sphingomyelinase

Group c) Claims 26-27 are drawn to method wherein the patient is suffering from Fabry's disease and gene therapy vector encodes alpha-galactosidase

Group d) Claims 28-29 are drawn to method wherein the patient is suffering from Pompe disease and gene therapy vector encodes alpha-glucosidase

Group e) Claims 30-31 are drawn to method wherein the patient is suffering from Hurler's Disease and the gene therapy vector encodes alpha-L-iduronidase.

As stated in the previous restriction requirement filed on 2/06/01, in the instant case the inventions of the groups a-e are drawn to methods of treating different diseases- Gaucher's disease, Nieman Pick disease, Fabry's disease, Pompe disease and Hurler's disease. It is noted that the combination of treating one disease can not be used for treating another disease because every disease is caused by the deficiency of a different gene and therefore, each disease requires the administration of different protein or a gene encoding the protein. For example, a subject having Gaucher's disease cannot be given sphingomyelinase protein or a nucleic acid encoding sphingomyelinase. This will be true with every other disease. Moreover, each disease has a different replacement gene therapy method using biochemically and biologically different proteins that will require separate and non-coextensive search in the patent and non-patent literature.

Of the newly amended claims, only claims 19-21, 26-27 and 32 reads on claims 7 and 12 which are drawn to method wherein the patient is suffering from Fabry's disease and the gene therapy vector encodes alpha-galactosidase A. In addition, Claims 7 and 19 link(s) inventions (a)-(e). Upon the

allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Therefore, the following office action is an examination on the merits of claims 7, 12, 19-21, 26-27 and 32.

Claim Rejections - 35 USC § 112-enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 12, 19-21, 26-27 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method for providing biologically active human alpha-galactosidase A in vivo administration into the cells of a Fabry individual an amount of adenovirus vector expressing human alpha-galactosidase A, wherein said method further comprising treating patient with biphoshonate and agents selected from the

group consisting of doxorubin, gamma glorubin, heavy metal salts and agents capable of blocking Fc receptors.

does not reasonably provide enablement for the method for treating any patient suffering from accumulation of any metabolite with macrophages, any macrophage depleting compound, such that apopotosis is induced and administering to the patient via any route any gene therapy vector encoding any compound which is able to break any accumulated metabolite.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claim

With respect to the elected invention, the claims are directed toward a method for treating patient's suffering from accumulation of metabolite within macrophages, said method comprising treating the patient with a macrophage depleting compound, such that apoptosis of macrophages is induced, and

administering to the patient a gene therapy vector encoding a compound which is able to break down the accumulated metabolite.

The claims further limit to patients suffering from lysosmal storage disease preferably Fabry's disease, the gene therapy vector is limited to an adenoviral vector encoding alpha-galactosidase, the macrophage deleting agent is further limited to bisphosphonate.

The following aspects considered broad: a method to treat any patient suffering from accumulation of any metabolite wherein the said method comprising treating with any macrophage depleting compound and administration via any route to the patient any gene therapy vector encoding any compound which is able to break down any accumulated metabolite. As will be shown below, these broad aspects are not enabled for their full scope embraced. The detail of the disclosure provided by the Applicant, in view of the prior Art, must encompass a wide area of knowledge to enable one of ordinary skill in the art at the time of the invention to practice the invention without undue experimentation. However, as it will be discussed below this undue experimentation has not been overcame by the as-filed application. And, due to such lack of enablement, some claims are not enabled whatsoever.

State of the prior art

The claims are broadly drawn and fully encompasses a enzyme replacement therapy method to treat patients suffering from lysosomal storage disease and/or

from metabolite accumulation within the macrophages. However, at the time the application was filed 2/06/2001, state of the art in regards to using gene therapy methods to treat lysosomal storage disease such as Fabry disease was considered unpredictable. The unpredictability of treating patients' suffering from Fabry disease is exemplified in the following cited references: Schiffman R et al (Drugs 2002: 62 (5):733-742), Siatskas C et al (J. Inherit Metab. Dis. 23 (suppl. 2) (2001): 25-41 and Desnick RJ (J. inherit. Metab Dis. 24 (2001): 251-265. Schiffman states that enyzyme replacement therapy (ERT) reverses manifestations but does not effectively treat the neurological complications and that long-term studies are necessary to evaluate the full potential of ERT (see Abstract). Schiffman states that Fabry disease is a multisystem and multiorgan disorder associated with progressive damage and functional loss. Furthermore, Fabry disease resembles processes such as atherosclerosis rather than classical storage disorder, with a reduced likelihood of functional reversal once primary defect is reversed (see p. 735 1st column 4th ¶). In addition, Schiffman demonstrates the unpredictability and inconsistency of results from two trials using the same composition, alpha-galactosidase A. Shiffman states, "At this point, one cannot determine whether the different results are due to qualitative difference of alpha-galactosidase A made in human cells from the one made in Chinses Hamsters ovary or to a different clinical trial design and the patient population studies or a combination of both factors". Lastly, Schiffman highly recommends the requirement of long-term studies to evaluate the effects of ERT on critical clinical endpoints such as time to end-stage renal disease, cardiac

insufficiency, stroke, quality of life and survival rate (see p. 737 1st column 3rd and 4th ¶). Siatska C et al in corroborration states that while gene therapy methods for Fabry disease is encouraging, many of these initial studies have been of a "proof-of-principle" nature, however, and need substantial refinements prior to possible clinical utility and that there are nontrivial gene transfer vector production and qualification issue to be overcome before clinical trials can be undertaken (see p. 35 1st ¶). Lastly, Desnick describes that the associated immune response to the vector encoded proteins after a single administration and that much research will be required to achieve the goal of safe and effective gene therapy methods. In view of the totality of cited references, it would have unpredictable to one ordinary skilled in the art to reasonable expect to treat patient's suffering from Fabry's disease using any gene vector expressing any compound in combination with any macrophage depleting compound as therapy.

State of the prior art, at the time of the invention, in regards of gene therapy methods vacillates between two major problems of opposite poles. One is a problem of efficient gene delivery. For instance Verma et al. (Nature, 1997, Vol. 389 pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al. state that the ongoing problem is the inability to deliver gene efficiently and to obtain sustained expression. However, as the art inches towards success of novel delivery systems and methodologies, a safety issues arises. There is an increasing problem with safety issue regarding the use of chromosomally integrating viral delivery systems relates to the possibility of integration of the delivered gene of interest into a potential oncogene, known as

insertional mutagenesis. Vanin et al. (J. Virol. 1994, Vol.,68, no. 7 p. 4241-4250) teach that three of the ten monkeys developed fatal lymphomas following transplantation with retrovirus-transduced, autologous bone marrow progenitor (CD 34+) cells. The explanation for the death of these animals was that replication competent retroviruses (RCR) had arisen by two distinct recombination events during vector production. These viruses infected monkey T-lymphocytes and induced tumors by insertional mutagenesis. One event involved recombination between vector coding sequences and the helper packaging sequences, resulting in RCR formation. Despite many improvements, Chong et al. (J. Virology, 1998, Vol. 72 pp. 2663-2670) in the design of retroviral vectors and packaging cell lines, generation of RCR still occurs. Furthermore, the recent clinical trial of □c mediated gene therapy for X-linked severe combined immunodeficiency (X-SCID) has proven the potential of retroviral mediated gene transfer for the treatment of disease. However, it has also illustrated the potential dangers and unpredictability involved with such treatments due to insertional mutagenesis. To date and the date of the as-filed application, the art regarding the treatment of Fabry disease and/or lysosomal storage disease with conventional gene therapy vectors administered to patient is unpredictable.

The predictability or lack thereof in the art

The predictability or lack thereof in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the

subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art.

Guidance in the Specification and working example
Analysis of Quantity of Experimentation

The applicant claims broadly that by simply expressing gene therapy vector encoding any compound in patients having any of the contemplated lysosomal storage diseases with a macrophage deleting compound, an effective treatment can be generated. The as-filed application provides sufficient guidance only to the extent of providing biologically active human alpha-galactosidase A in vivo administration into the cells of a Fabry individual an amount of adenovirus vector expressing alpha-galactosidase A, wherein said method further comprises treating patient with clondronate.

The issue is whether or not any gene therapy vector encoding any compound in combination with any macrophage depleting compound can be reasonably extrapolated to the full breadth of the claimed invention to treat a patient suffering from accumulation of any metabolite with macrophages or those suffering from lysosomal storage disease. A person skilled in the art would have not reasonably extrapolate such without any undue experimentation because of a number of obstacles as expressed above by the art of record. For example, Siatskas et al states the obstacles and difficulties to transduced cells, issue that

remain concerning development of uniform packaging cells for lentivirus, potential cross-activation/recombination with wildytpe human viruses and the obstacle to the preparation of large amounts of clinical grade vector (see p. 29 2nd ¶). Bainbridge et al (Clinical Science (2003) 104, p. 561-575) states that although adenoviral vector efficiently target cells of the outer retina, their duration of expression is limited by immune responses to the vector (see p. 566-567 last paragraph). In addition to the problems inherently lied within a particular disease itself under the context of gene therapy, the Prior Art teaches the unpredictable use of adenovirus vectors as therapy and the need for continued experimentation in the clinical setting (Bromson et al. and Tjuvajev et al.). Relph et al. (Seminars in Oncology 2005 573-582) teach that there are certain guidelines to provide the viral load and PFU such pfu/kg or viral particles/kg. However, there are no working examples or guidance in the specification in terms of the steps, mode of administration, patient characteristics, dose of virus, timing such as to provide to one skilled in the art to make and use the invention commensurate in scope with these claims other than those pertaining to adenovirus vector expressing human alpha-galactosidase.

In view of the unpredictability of the Art, it is essential to provide sufficient description and/or guidance in the specification the method of treating patients suffering from accumulation of a metabolite with macrophages such as those suffering from lysosmal disease with the claimed gene therapy vector expressing any compound able to break down the accumulated metabolite. However, Applicant provides no detail of the broad scope commensurate of the claims.

Therefore one skilled in the art would have to perform undue experiment to make and use the full breadth of claimed invention. Therefore, Applicant provides insufficient guidance and /working example for a skilled artisan to reasonably enable the claimed invention of a method of treating patients with lysosmal storage disease with gene therapy vector which expresses any compound that is able break down the accumulated metabolite.

In order to practice the claimed invention particularly in light of the prior art and guidance or lack thereof, one skilled in the Art would not find it reasonably enabled to treat a patient with intended disease with the claimed gene therapy vector and any macrophage depleting compound. In light of the unpredictability of the state of art with respect to treating such diseases with retroviral or adenoviral-associated vectors wherein the totality of the cited references exemplifies the obstacles of induction intraocular inflammation, mutational mutagenesis, the ability to control or regulate the release of protein of interest and the consensus that experimental and preclinical studies must be conducted. Due to the large quantity of experimentation necessary to effectively treat any patient suffering from accumulation of a metabolite macrophages such as those suffering from lysosomal storage disease preferably Fabry Disease, one skilled in the Art will have to perform extensive experimentation with each of these parameters to find the embodiments embraced by the claims, and as such, this experimentation would be considered undue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section in this Office action:

A person shall be entitle to a patent unless-

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19 is rejected under 35 U.S.C 102(b) as being anticipated by Stein CS et al (Gene Therapy 1998 Apr;5 (4):431-439). Stein et al teach a method of adminstration of a recombinant adenovirus expressing a transgene and clodronate to study the prolonged transgene expression after primary adenoviral vector administration and increase efficieny of redosing to the liver (see p. 432 1st column 1st ¶). Stein et al teaches Clodronate is a macrophage depleting compound that administrated in combination with adenoviral vector expressing transgene of interest, depletes macrophage and enhances the amount of transduction of the adenoviral vector expressing transgene of interest (see p. 432, Result section 1st ¶). Stein specifically teaches that injection of clodornate liposomes before vector infusion may reduce the immune response. In addition, Stein states that liposomes incorporating the drug "clodronate" are phagocytosed by and subsequently kill haptic Kupffer cells and splenic macrophages (see p. 432 1st ¶). Therefore, as set forth above, Stein et al teaches claimed invention of first administering and effective amount of macrophage inhibiting agent following by administration of adenovirus vector.

Fabry Disease and administrating a macrophage depleting compound, clodronate, since Stein CS et al teaches potentiating effects of clodronate in combination with adenoviral expressing transgene based therapies. Thus, the invention embraced by the claims was prima facie obvious.

Claims 19, 21 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein CS et al (Gene Therapy 1998 April 5 (4):431-439) and in view of Daemen T et al (Int. J. Cancer 1995 61 (5):716-21).

The teachings of Stein are presented above. However, Stein et al does not teach the administration of a macrophage inhibiting agent such as doxorubin.

However, Daemen et al teaches the administration of doxorubin into rats wherein phagocytic capacity was determined by isolating the liver macrophages and measuring the amount of macrophage-associated activity.

Accordingly, it would have been obvious for one ordinary skilled in the art to employ the methods and concept of using an adenoviral vector expressing transgene of Stein et al in combination with a macrophage depleting compound such as doxorubin to promote the inhibition or depletion of macrophage. At the time of the invention, one ordinary skilled in the art would have been motivated to incorporate the teaching of the primary reference with administration of Doxorubin because Daemen et al demonstrated that after injection with lip-Doxorubin, the phagocytic capacity of the larger-sized liver macrophages was strongly decreased. One ordinary skilled in the art would have been motivated to combine the two methods because one ordinary skilled in the art would have reasonably expectation of success since Deamen et al teaches that when after

Accordingly, it would have been obvious for one ordinary skilled in the art to employ the methods and concept of using an adenoviral vector expressing alpha-galactosidase of Yew et al in combination with a macrophage depleting compound such as clodronate to promote the inhibition or depletion of macrophage and its accumulated metabolites. At the time of the invention, one ordinary skilled in the art would have been motivated to incorporate the teaching of the primary reference with administration of Clodronate because Stein demonstrated the use of adenoviral vector expressing transgene of interest in combination with clodronate that macrophage deleption enhanced the amount of transduction (see p. 432, Result section 1st ¶). One ordinary skilled in the art would have been motivated to combine the two methods because one ordinary skilled in the art would have reasonably expectation of success since it is very well known in the art that when administered systemically, liposomes incorporating the drug "clodronate" are phagocytosed by and subsequently kill hepatic Kupffer cells and splenic macrophages (see p. 432 1st ¶). As such, the combined cited references teaches the potentiating effects of using adenoviral vectors encoding transgenes of interest and applying clodronate which are known to one ordinary skilled in the art to be able to deplete macrophages thereby release accumulation of any stored metabolite. Therefore, one of the ordinary skilled in the art would have a reasonable expectation of success in practicing the methods and concepts set forth by the combined cited references since the totality of the prior teaches the effectiveness of administrating adenoviral vectors encoding alpha-galactosidase in cells of individuals with

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19, 26 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein CS et al (Gene Therapy 1998 April 5 (4):431-439) and in view of Yew et al (Patent No. 6066626, May 23, 2000).

Stein et al teach the method combination of a recombinant adenovirus expressing a transgene and clodronate to study the prolonged transgene expression after primary adenoviral vector administration and increase efficieny of redosing to the liver (see p. 432 1st column 1st ¶). However, Stein et al does not teach the invivo administration of adenoviral vector expressing alpha-galactoside to individuals with Fabry Disease.

However, Yew teaches method for providing biologically active human alpha-galactosidase A to cells of an individual with Fabry disease comprising in vivo administration into the cells of a Fabry individual an amount of pCFA-hAGA effective to transfect and sustain expression of biologically active alpha-galactosidase A (see claims 1-2 and 8-13 and see examples 7 and 8). In addition, Yew further teaches the method wherein a viral vector specifically adenoviral vector expresses alpha-galactosidase.

injection with doxorubin, a major depletion of liver macrophage population is observed as revealed by both macrophage isolation and histology. As such, the combined cited references teaches the potentiating effects of using adenoviral vectors encoding transgenes of interest and applying doxorubin which are known to one ordinary skilled in the art to be able to deplete macrophage thereby release accumulation of any stored metabolite. Therefore, one of the ordinary skilled in the art would have a reasonable expectation of success in practicing the methods and concepts set forth by the combined cited references since the totality of the prior teaches the effectiveness of administrating adenoviral vectors as a method of gene therapy and administrating a macrophage inhibiting agent such as doxorubin, since Daemen et al teaches potentiating effects of doxorubin in depleting or inhibiting the phagocytic activity of macophages. Thus, the invention embraced by the claims was prima facie obvious.

Claims 7, 12, 20 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yew et al (Patent No. 6066626, May 23, 2000), and in view of Stein CS et al (Gene Therapy 1998 April 5 (4):431-439).

Yew teaches method for providing biologically active human alpha-galactosidase A to cells of an individual with Fabry disease comprising in vivo administration into the cells of a Fabry individual an amount of pCFA-hAGA effective to transfect and sustain expression of biologically active alpha-galactosidase A (see claims 1-2 and 8-13 and see examples 7 and 8). In addition, Yew further teaches that the method wherein a viral vector specifically

adenoviral vector expresses alpha-galactosidase. However, Yew et al does not teach the administration of macrophage depleting compound, clodronate.

However, Stein et al teach the method combination of a recombinant adenovirus expressing a transgene and clodronate to study the prolonged transgene expression after primary adenoviral vector administration and increase efficieny of redosing to the liver (see p. 432 1st column 1st ¶).

Accordingly, it would have been obvious for one ordinary skilled in the art to employ the methods and concept of using an adenoviral vector expressing alpha-galactosidase of Yew et al in combination with a macrophage depleting compound such as clodronate to promote the inhibition or depletion of macrophage and its accumulated metabolites to patients suffering from Fabry Disease. At the time of the invention, one ordinary skilled in the art would have been motivated to incorporate the teaching of the primary reference with administration of clodronate because Stein demonstrated the use of adenoviral vector expressing transgene of interest in combination with clodronate that macrophage deleption enhanced the amount of transduction (see p. 432, Result section 1st ¶). One ordinary skilled in the art would have been motivated to combine the two methods because one ordinary skilled in the art would have reasonably expectation of success since it is very well known in the art that when administered systemically, liposomes incorporating the drug "clodronate" are phagocytosed by and subsequently kill hepatic Kupffer cells and splenic macrophages (see p. 432 1st ¶). As such, the combined cited references teaches the potentiating effects of using adenoviral vectors encoding transgenes of

interest and applying clodronate which are known to one ordinary skilled in the art to be able to deplete macrophage thereby release accumulation of any stored metabolite. Therefore, one of the ordinary skilled in the art would have a reasonable expectation of success in practicing the methods and concepts set forth by the combined cited references since the totality of the prior teaches the effectiveness of administrating adenoviral vectors encoding alpha-galactosidase in cells of individuals with Fabry Disease and administrating a macrophage depleting compound, clodronate, since Stein CS et al teaches potentiating effects of clodronate in combination with adenoviral expressing transgene based therapies. Thus, the invention embraced by the claims was prima facie obvious.

In conclusion, all claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malou C. Gemeniano whose telephone number is 571-272-6451. The examiner can normally be reached on 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jabobs, whose telephone number is (571)-272-0532.

For all other customer support, please call the USPTO Call Center (UCC) at (800)-786-9199.

Malou C. Gemeniano, Ph.D
Examiner, USPTO, AU 1632

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER

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